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EMVI and Extra Nodal Deposits; Should They Be Treated The Same?

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Abstract

Professor Nagtegaal had already highlighted that lymph nodes were probably not responsible for the development of liver metastases. If they are not, then is there another mechanism? Professor Haboubi addresses the question of extranodal deposits – their frequency and their importance in the development of metastatic disease. The experts review the evidence and discuss whether this information will alter treatment decisions and staging systems in future.

To answer the question whether Extra Nodal Tumour Deposits (ENDs) and the Extra Mural Vascular Invasion (EMVI) should be treated the same, the following questions have to be answered: are they readily recognisable, are they related and can we delineate prognostics?

There is some confusion in the literature. The first area of confusion is the definition of ENDs, also known as tumour deposits (TD) which have been defined as "microscopic mesorectal or mesocolic soft tissue extranodal deposits which are discontinuous with the primary tumour [1]. There are contradictions in terms of the use of the words microscopic and also discontinuous as will be seen later.

Recognition and nature

There is disagreement in the literature about how often ENDs are demonstrated. Wang *et al* say they see ENDs in all cases of rectal cancer when they use the large slide mount [2]. But most authors don't see them that often and they are reported anywhere between 4.5-45% of rectal cancers and 17.6-25.5% of colon cancers.

What is the route of deposition i.e. how do ENDs breach the bowel wall? Is it through the vascular, perineural or lymphatic permeation, or indeed as direct deposits? The latter route exemplifies the first element of confusion, as according to the original description the deposits should be discontinuous

The critical paper from Nagtegaal *et al* speculates that the "origin of EMDs can be heterogeneous as they may represent true lymph node replacement"[3], which is again a contradiction to the original definition as an extra-nodular disease. They also speculated that they could be "vascular, lymphatic or perineural space invasion and often a combination of patterns"[3]. It is therefore difficult to delineate the prognostics in this particular area. There is however general agreement that ENDs are bad independent prognostic indicator with a hazard ratio for death from the disease at 1.96[3].

However there is a further challenge. The Duke's classification did not identify tumour deposits as a separate entity; they may have been thought to represent lymph nodes. This pattern may have been replicated where in old series of lymph node retrievals little deposits in the fat may have been regarded to be lymph nodes!

Overall the TNM position with regards to tumour deposits is bizarre. Initially TNM 5th edition definition depended on the size. If the nodule was ≤ 3 mm it was regarded as a tumour deposit, if >3 mm it was regarded as a lymph node, and therefore pN1. TNM version 6 recognised the contour and not the size. So that if the nodule is round - it should be considered as lymph node, if it is not round it is not a lymph node but a tumour deposit (and could represent venous invasion), which is either microscopic (V1) or macroscopically evident (V2). Yet again the macroscopic recognition of such lesions automatically contradicted the original definition of ENDs! TNM version 7 recognises ENDs as N1c.

Tumour deposits and lymph node status

In the published literature tumour deposits are seen in approximately one third to almost two thirds of lymph node negative cases. However there is always an agreement of bad prognosis irrespective of the stage of the disease.

Puppa *et al*/ proposed a more comprehensive classification approach in terms of the shape and involvement of other structures and described the prognostic implications of the 3 morphological variants namely vascular (lymphatic or venous), ENDs other than vascular or peri neural and thirdly EMVI and peri neural invasion type ENDs: They suggested that the presence of tumour deposits within the lymphatic or vascular space (i.e. T staging) is associated with an overall survival HR of 2.5. Tumour deposits of the non vascular invasion type are associated with poorer prognosis (HR 4.7, similar to lymph node metastases) and finally deposits with extramural venous and perineural invasion have the poorest prognosis [HR 8][4]. This paper highlights the various histological features and gives some prognostic indicators related to the pattern, however this does need to be validated.

Prebhudesai *et al* looked at 55 patients with Duke's B and C rectal cancer - 29 patients had ENDs (8 Duke's B) and 26 controls and showed that the presence of tumour deposits was associated with earlier distant metastases (14 months vs 37 months, $p=0.001$). There were significant increases in the incidence of liver metastasis (31.03% vs 11.5%, $p=0.08$), local recurrence (17.8% vs 3.8%, $p=ns$) and poorer 3 year mortality (16 vs 7 patients, $p=0.09$). The authors also showed there

was also an association with EMVI ($p=0.017$), perineural invasion ($p=0.039$) and lymph node involvement ($p=0.008$)[5].

Extramural venous invasion

There are problems with the recognition of EMVI and therefore problem with regards prognosis mostly due to the fact that pathologists vary in recognising EMVI. If we analyse synoptic reporting there are some pathologists who are very good in registering EMVI but if you showed the same slide to various pathologists you would get different readings and this is a problem.

Prof I. Nagtegaal showed that pathologists identify vascular invasion in about half of cases but in UK this figure varies significantly. In 1980 Talbot et al showed the same results. He also reported that intramural vascular invasion is important but not as important much as extramural vascular invasion and showed elegantly that these features are related to the lymph node metastasis, Duke's staging, liver metastasis and survival[6].

A more recent paper from the Concord Group in Sydney with 3040 patients reported that prognosis is stage specific and that both mural and extramural vascular invasion are independent predictors for poor prognosis, but only in Stage C disease (as classified by the ACP staging, Stage III)[7].

A recent paper by Chand *et al* gave, on evidence base, recommendations for radiological and histopathological reporting of EMVI. The authors emphasised what has been known that elastic tissue stains increase the yield of EMVI recognition. This may be difficult to implement given the variations in capabilities of the departments, but the use of specialised stained may reduce the variables for the recognition of EMVI. The authors also conclude that radiology (MRI) is at least as sensitive as histology in identifying EMVI, and has the benefit of being more dynamic and repeatable. MDTs need to keep auditing EMVI detection rates by both disciplines[8].

So to answer the question whether ENDS and EMVI should be treated the same, I would say probably yes, because some are interrelated, they are independently associated with lymph node metastases, poor survival and advanced staging.

Discussion

Dr M. Morgan: In terms of examining the pathological specimen it's really about good sampling, so looking for those extra nodal deposits. I'm not sure that as pathologists we are very good at picking [them] up. We don't examine all of the tumour all of the time.

Prof B. Heald: It seems to me that Prof G. Brown's paper and observations that the greatest prognostic indicator before surgery is the response to chemotherapy and radiotherapy [are important]. I'm not sure

whether it's the response to chemotherapy alone, that would be a good thing, but surely all our planning has to be dominated by a sequence of MRI followed by treatment followed by MRI, and at some point we have to decide which way we are going for responders or non-responders.

Prof D. Cunningham: I have an impression that we are over treating significant numbers of patients with rectal cancer. It is a spectrum, there are patients who have excellent prognosis with very early disease who just need a good operation and then there are some people with more advanced disease where you can use either chemotherapy or chemoradiotherapy as a means of determining biology/response and therefore outcome. I am assuming you are addressing that to the higher risk patients. What do the panel feel about using response to chemotherapy in higher risk patients as a way of evaluating outcome and biology.

Dr C. Fernandez Martinez: I think it is very important in the next generation of clinical trials to try to introduce patients in our trials with really high risk of relapse. MRI is a good tool to know which patients are high risk. Extramural venous invasion is probably the most important predictive factor for metastatic disease and CRM [positivity]. We

must introduce this kind of information in order to treat the right patients in the next generation of clinical trials.

Prof C. Eng: I understand what you're saying if we are specifically talking about rectal cancer but it doesn't apply to all cancers. All the trials that have looks at pathCR have varied everywhere from 5% to 35% but that does not result in increased overall survival. I just want to make sure that we keep in mind that although you have a great response upfront in terms of path CR that that may not help down the [line] and there may be more of a sequencing issue there.

Prof D. Cunningham: Can I come back to EMVI, which is one of the conversations in our MDT in relation to rectal cancer. Is EMVI more important than anything else and should it be the primary determinant of how we manage patients in terms of upfront chemotherapy and post-operative chemotherapy? This is one of the challenges that I face as an oncologist, we know that actually adjuvant chemotherapy is of some benefit in these patients, the incremental gain is not that great but should we use EMVI as the driver for [treatment]?

Dr P. Nilsson: I don't know the answer to that but I think that it is complicated because in rectal cancer we have two almost equally important endpoints, local and systemic control, and it depends on what you are aiming for. You want to get good results for both. EMVI might be important for systemic control but does it have any effect on local control?

Dr C. Fernandes-Martinez: Systemic relapse is important in high-risk rectal cancer. Surgeons have very little local relapse but systemic relapse is more of an issue (30% in 5 years). Chemotherapy as optimum systematic treatment must be applied. To move forward the induction strategy is a good idea. [It is] also [important] to know which [patients] need radiotherapy or just need chemotherapy. Those with EMVI positivity are probably best treated with just chemotherapy rather than chemoradiation as local relapse [rates are] very low.

Audience: When do you think it is best operating after chemoradiation and what do you think the mechanisms for better outcome are if we operate later, because it seems counterintuitive leaving the tumour in place for longer and then taking it out, assuming that you're getting the same operation. Why is it that you get better survival by taking it out late? In addition the new trials of neoadjuvant chemotherapy don't have

the radiotherapy component e.g. BACCHUS, are there any reservations on leaving out radiotherapy?

Prof D. Cunningham: What is the best time [to operate]? Is it at the standard time, which is 4-6 weeks, or should we wait longer? What are the gains and what could we lose?

Dr P. Nilsson: I get the impression that we are learning to wait longer and longer, how long we should wait and what is optimal is yet to be found out.

Dr A. Mirzenami: The difficulty is that tumours are very heterogeneous and their response to treatment is also extremely heterogeneous. So it is very difficult to have standardisation on how long we leave it for different patients.

Prof G. Brown: Just a point on pelvic recurrence in patients with EMVI. The problem we have is that most patients with EMVI do have characteristically classically defined advanced disease, and even in some of these trials they're probably not the ones that are being treated with primary chemotherapy. There are a few

studies but [they haven't recruited patients with very] advanced EMVI.

If you look at the ACCORD data there is a relationship between the risk of EMVI positivity and CRM positivity. They're linked and the reason for this is probably that once the tumour has got into the vessel the vessel itself does not respect the mesorectal envelope or boundaries, unlike lymph nodes which confine themselves to within the mesorectum, there is therefore a mechanism for lateral spread to the pelvic sidewall compartments. So the other piece of evidence about avoiding radiotherapy in EMVI positive patients is the strong positive link between pelvic sidewall nodal metastases and EMVI that we may be masking by the use of radiotherapy. These patients do not relapse with pelvic lymph node recurrence because of the protective effect of the radiotherapy. So we have to be careful that this late development after treatment may only emerge and will be masked by the path CR rates.

Prof J. Nicholls: This is a question to the pathologists. Could the failure to find lymph node deposits be technical? It would be interesting to hear, given the size of tumour cells and indeed the thickness of sections taken, the view of the pathologist as to whether [it would be worth looking further for these deposits] where we

could be finding very small metastatic disease which is [actually] biologically insignificant.

Dr M. Morgan: In terms of looking for lymph nodes the biggest problem I get is that we haven't found 12 lymph nodes and clearly it is an important question. We look hard for them using [multiple methods]. There is some evidence that the more you look you don't find [more positive] nodes. Unlike in breast cancer we are not looking very hard for microscopic deposits, this would mean a lot of extra work.

Concept 2: TNM staging

Prof G. Brown: One more comment from Prof M. Mason about TNM, from what [you've] heard this morning do you think the TNM classification needs modification?

Prof M. Mason: Under the current c TNM-7 classification the distinction between N1a and N1c is subjective and unreliable. The reason [we haven't changed it] is because we have not yet heard articulated a convincing argument that it really matters. Through the whole TNM classification [there are] areas where things are subjective and unverified. What I particularly want to hear is the voice of the oncologists, I want to know whether there is evidence that

for a [single] patient, the distinction between N1a and N1c as the sole determinant makes a real difference to a treatment decision. The clinical opinion we currently have [says it's] not a perfect classification but that it does not matter than much from the point of view of making major treatment decisions.

Dr M. Morgan: Following on from what Professor Malcolm Mason has just said, the second objective was “Do we need to overcome the shortcomings of a TNM system? Do we recognize that there are problems with it? And if so, what do need to do about it? How do we make that better? How do we propose improvement in TNM?”

Prof D. Cunningham: Also if some of our oncologists could comment on whether there is a real difference between an N1a and N1c and how that might influence what they do.

Prof M. Berho: The TNM system is not [perfect] but it has very good parts and we need to acknowledge that. Actually, the anatomical extent of the disease is very important for the oncologist to make treatment decisions so to just dismiss it is probably inappropriate. The TNM committee has recognized the flaws of the system and it is continuously trying to enhance it, in the last

edition, several other factors besides the classic pT and pN [stage] are mentioned, including certain critical molecular markers that influence prognosis and treatment, such as MSI status and KRAS mutation analysis.

Although it is very possible that the mechanism of distant metastasis is, in some cases, independent of lymph node metastasis, it is also important to point out that not all lymph node metastasis are recognized, either due to an inadequate number of lymph nodes examined, as well as the presence of metastatic disease that requires ancillary techniques to be identified. It has been shown that micro metastases are associated with a more clinical aggressive outcome.

Audience: I am a surgeon, from my point of view, it's a big problem if you continuously modify small bits and pieces where there is no evidence that it is reliable and that it matters. [This is a problem for] long term prospective registries.

Audience: [It is] important that we change therapies based on evidence; on clinical trials, randomized trials, high levels of evidence. But [over the last 15 years we have been] changing TNM [without an] evidence-[base]. [This is a problem because as] you change

staging, you change [which] people are treated treatments you have tested for other stages.

Prof M. Mason: Absolutely you do not want to change TNM unless there is evidence behind it.

Dr M. Morgan: We are not going to get the evidence while we are all doing different things.

Audience: I fully agree. I use TNM everyday in my clinic so that's very useful and I'm against changing that, but me the important issue is that TNM is based upon the consequences of the disease. There is nothing we can modify. So it is a very anatomic concept and we need to incorporate new knowledge into that by incorporating those pathogenetic mechanisms that are important.

I would therefore like to better understand the development of metastatic disease and then to incorporate those factors into clinical decision [making].

Summary of the key points

- The pathological identification of extra nodal deposits is challenging and relies on good sampling. Elastin stains enhances such recognition.
- ENDs are bad independent prognostic indicators and may be secondary to “vascular, lymphatic or perineural space invasion and often a combination of patterns”[3].
- Tumour deposits are seen in approximately one third to two thirds of lymph node negative cases.
- Tumour deposits with extramural venous and perineural invasion have the poorest prognosis.
- MRI is at least as sensitive as histology in identifying EMVI, and has the benefit of being more dynamic and repeatable. MDTs need to keep auditing EMVI detection rates by both disciplines
- ENDs and EMVI should be treated similarly. They are independently associated with lymph node metastases, poor survival and advanced staging.
- It is possible that EMVI may be a better primary driver for the use of systemic treatment.
- Systemic relapse is a greater issue than local control, induction treatment could be considered, and it will be important to know whether patients need chemotherapy, radiotherapy or both.
- EMVI may be best treated with chemotherapy rather than chemoradiotherapy

as local relapse rates are low. However EMVI positivity and CRM positivity are linked and EMVI positivity is associated with lateral spread into the pelvic side wall. The current use of radiotherapy to treat patients EMVI may be obscuring the true prevalence of pelvic side wall metastases.

- The distinction between N1a and N1c disease in TNM-7 is subjective and unreliable but in order to change it studies are required to show this distinction is a sole determinant for treatment decisions.

Audience voting

Question: Extranodal tumour deposits are a high-risk feature associated with EMVI

Strongly agree: 41%

Agree: 43%

Neutral: 11%

Disagree: 3%

Strongly disagree: 2%

Question: Extranodal tumour deposits should be documented

Strongly agree: 60%

Agree: 35%

Neutral: 2%

Disagree: 1%

Strongly disagree: 2%

Question: Is it worth considering EMVI as a driver for adjuvant therapy decisions.

Strongly agree: 30%

Agree: 47%

Neutral: 11%

Disagree: 2%

Strongly disagree: 1%

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